Application No. 10/762,964
Filed: January 22, 2004
TC Art Unit: 1618
Confirmation No.: 6339

REMARKS

Claims 1-18 are pending. Claims 1-18 are rejected as allegedly anticipated, obvious, or containing new matter. Reconsideration of the rejections is requested based on the comments presented below.

Double Patenting

Claims 1-18 are rejected on the grounds of nonstatutory obviousness-type double patenting. The present claims allegedly overlap with the claims of the parent, U.S. 6,726,896. The rejection is traversed.

The claims of the '896 patent are directed to liquid formulations of a stool marker composition and methods of using the liquid formulations. The present claims are directed to solid formulations of a stool marker composition and methods of using the solid formulations. The restriction requirement issued in the parent case (mailed July 21, 2003 as Paper No. 17), which eventually issued as the '896 patent, established the liquid formulations and the solid formulations as separate inventions. The liquid formulation claims were considered as Invention I ("Claims 45-47, 52-62, 80-91 and 103-108, drawn to a liquid stool

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marker comprising barium sulfate in a specific % amount and methods of imaging using said marker"), while the solid formulations were considered as Invention IV ("Claims 63-65, 70-79 and 92-102, drawn to a solid stool marker comprising barium sulfate"). As reason for the distinction, the Examiner argued that the amount of the radio-opaque material present "in the liquid formulation (e.g., 0.5-3%) is greatly different than the amount in the solid formulation (e.g., 95%)."

The present obviousness-type double patenting rejection is inconsistent with the restriction requirement in the parent case, which maintained that similar claims directed to solid formulations were independently patentable compared to the liquid formulation claims that issued in the '896 patent. Further, since the Examiner of the '896 claims admitted that the barium sulfate content of the liquid formulations is "greatly different" than that of the solid formulations, it follows that the present solid formulation claims are not obvious over the liquid formulation claims of the '896 patent. The withdrawal of this rejection is respectfully requested.

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Rejection Under 35 U.S.C. 112, First Paragraph

Claim 1 is rejected for allegedly reciting new matter in the limitation "wherein 0.25 g of solid stool marker formulation is diluted with water to 50 mL". The specification indicates 2.5 g instead of 0.25 g of the solid formulation. The rejection is respectfully traversed.

The flocculation resistance test in the first footnote to Table I mentions 2.5 g of the solid formulation as being 10% of a typical dose. This is a typographical error, and has been corrected by amendment to read "0.25 g" which is in fact 10% of the typical dose of about 2.5 g. Support for this amendment can be found at page 10, line 26, which discloses 2.4 g of powder as the total dosage, and at page 12, lines 17-19, which talks about four 600mg capsules or powders constituting a dose. Further, it would be apparent to a person skilled in the art that 2.5 g of solid formulation would be an appropriate total dose, not just 10% of the total dose, because at page 3 the specification states that the absolute dosage of $BaSO_4$ does not exceed 6 - 7.5 g. In light of the recitation of 0.25 g of solid formulation for the flocculation resistance test in the amended specification, the new matter rejection is moot.

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Rejection Under 35 U.S.C. 102(b)

Claims 1-4, 6-8, and 10 are rejected as allegedly anticipated by Brown US 3,236,735. The rejection is respectfully traversed.

Brown teaches the use of barium sulfate in a conventional X-ray contrast agent suitable for imaging the walls of the gastrointestinal system. The present claims are not directed to a conventional contrast agent, however. The present claims are directed to a stool marker, which is very different from a conventional contrast agent. Normal contrast agents need a substantially empty bowel, and coat the mucosal surface thereof. They require a highly disperse contrast agent. Stool markers are incorporated in stool and provide an image of stool, not the mucosal surface. To achieve this, the contrast agent must be flocculative, rather than dispersed. The conventional contrast agents disclosed by Brown are specifically designed to disperse barium sulfate in the intestine. However, the stool marker of the present claims is designed to flocculate barium sulfate in the intestine.

Thus, Brown's compositions differ from those of the present claims in requiring high levels of dispersants to ensure that the barium sulfate does not agglomerate or flocculate. In contrast, the compositions of the present claims are

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substantially free of ionic dispersants, which would prevent the flocculation of barium required to mark the stool.

The formulations of the present invention work in a different manner from previous formulations, including those of Brown. This is manifested in the substantial absence of ionic dispersants from the present formulations, as well as in the low flocculation resistance value recited in the present claims. The claims specify that, at a certain barium sulfate level, (0.5 to 3%) then the formulation must have a corresponding upper limit of ionic dispersants (less than 0.035N) and have an overall low flocculation resistance with reference to specifically defined ferrous sulfate test.

In the present formulations the contrast agents incorporate into the stool, allowing it to be imaged. By imaging the stool, a high quality picture of the surrounding bowel can be generated. This is only possible by having the barium sulfate contrast agent agglomerate or flocculate. Formulations such as found in Brown, which rely upon achieving high dispersion of barium sulfate, work in a different way. In those more typical formulations, the bowels of the patient need to be emptied and the highly dispersed barium sulfate formulation is then introduced into the empty body cavity where the contrast agent

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formulation coats the walls. The imaging process then allows the coated walls to be imaged.

Brown discusses the criticality of using a viscosity modifier to increase the fluidity of barium sulfate suspensions at column 1, line 31 to 39:

> [T]he fluidity of barium sulfate suspensions is much improved and the preparation greatly facilitated by including in the aqueous medium a non-toxic fluidising agent consisting of a water-dispersible colloidal salt of an ionic ether or ester derivative of a low polymer of a monosaccharide such as a water soluble salt of an anionic ether or ester derivative of a low polymer glucan.

That is, Brown relies upon the presence of ionic dispersants to control the fluidity of barium sulfate. Brown states at column 3, lines 21 onwards, that: "The function performed by the fluidizing agents in the present invention is to prevent agglomeration of the barium sulfate particles during preparation of the suspension". This is a teaching specifically away from the highly agglomeration-prone preparations of the present invention. The present invention uses compositions that are free or substantially free of ionic dispersions. The present claims recite compositions having a very low level, between 0 and less than 0.35N, of ionic dispersants when the solid formulation is diluted to the test range specified in the claims.

The Office Action notes that there are no limitations on

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the amount of barium sulfate or flocculant in the present claims, and that any composition can be diluted to give the claimed range of barium sulfate. Applicant points out that the claims specify that, at a certain barium sulfate level, (0.5 to 3%) the formulation must have a corresponding upper limit of ionic dispersants (less than 0.035N). Further, the claims specify that the formulation must have an overall low flocculation resistance with reference to a specifically defined ferrous sulfate test.

The Office Action points out that Brown teaches formulations comprising both barium sulfate and bentonite, a flocculant. Brown teaches bentonite for only one purpose, at column 4, line 55, which is to retard settling of the barium sulfate prior to administration. Brown notes that bentonite "unfortunately" and "undesirably" increases flocculation. Bentonite is only exemplified in example 3, and it can be seen that significant amounts of an anionic dispersant, Sodium CMC, are present. Anionic dispersants in significant amounts are expressly excluded by the present claims. Clearly, the composition in Brown is formulated to be useful in the particular contrast methods disclosed therein, i.e. to have dispersed barium sulfate, not agglomerated barium sulfate.

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Further, on inspection of the overall formula, a person skilled in the art would clearly expect the formula to disperse, rather than flocculate. Brown has relatively high levels of dispersant in all examples. Brown has a small amount of flocculant in just one case, Example 3, which is offset by dispersants at a level not permitted by the present claims.

Brown fails to disclose a solid composition comprising barium sulfate and a flocculant, wherein the composition, if dissolved to form a solution with 0.5 to 3% w/v of barium sulfate, has less than 0.035N ionic dispersant, and wherein 0.25 g of the solid formulation, if dissolved in water to 50 ml and titrated with ferrous sulfate at pH 5.0-5.5, has a flocculation resistance of less than 5ml. Therefore, Brown does not anticipate the present claims. Withdrawal of this rejection is respectfully requested.

Rejections Under 35 U.S.C. 103(a)

Claims 1-4, 6-8, and 10-16 are rejected as allegedly obvious over Brown US 3,236,735 in view of Queuille US 4,120,946. The rejection is respectfully traversed.

As indicated above, Brown teaches neither the low quantities of ionic dispersants nor the resultant high levels of flocculation that are exhibited by the stool marker formulations of the present

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application. The combination of Brown and Queuille ultimately fails to provide any teaching or suggestion of a composition or method employing a low levels of either ionic dispersants or flocculation resistance. The combination of Brown and Queuille can only ever teach compositions and methods that avoid flocculation, because both references teach the importance of having the barium sulfate suspended, not flocculating. The present invention relies upon having a mixture which has a very low resistance to flocculation. Both Queuille and Brown teach specifically the importance of keeping the barium sulfate dispersed; therefore, this combination of references clearly teaches away from the requirement from the present application to have flocculation prone solutions.

The Office Action asserts that the combination of Brown (teaching barium sulfate and bentonite) with Queuille (teaching barium sulfate, xanthan gum, and citrate) renders obvious the present claims, one embodiment of which (see, e.g., claim 11) is a combination of barium sulfate, smectite clay, xanthan gum, and citrate. However, Queuille teaches no composition including a flocculant such as clay, and Brown only teaches adding a small amount of bentonite if in the presence of a substantial amount of an ionic dispersant. If the teachings of Brown and Queuille are

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combined, the result will be as deficient with respect to avoidance of ionic dispersants and flocculation resistance as Brown is alone. That is, Queuille does not cure the defect of Brown; Queuille merely adds additional components such as xanthan gum and citrate in the context of the highly dispersive and flocculation avoiding formulations of Brown, which do not fall within the present claims.

This rejection is further defective when method claims 12-15 are considered. These claims require the step of "manipulating the data to determine that portion of the data due to marked stool" which clearly cannot be performed based on any teaching or suggestion found in either Brown or Queuille. None of the compositions or methods in either reference would specifically mark the stool.

The cited references, either alone or in combination, fail to disclose a solid composition comprising barium sulfate and a flocculant, wherein the composition, if dissolved to form a solution with 0.5 to 3% w/v of barium sulfate, has less than 0.035N ionic dispersant, and wherein 0.25 g of the solid formulation, if dissolved in water to 50 ml and titrated with ferrous sulfate at pH 5.0-5.5, has a flocculation resistance of less than 5ml. The references either alone or in combination also

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fail to disclose a method of using such a composition either to prepare a patient for radiological examination or to mark the stool so as to provide a representation of the colon. Therefore, because the combination of references fails to teach every limitation of the present claims, the references do not render the present claims obvious. Withdrawal of this rejection is respectfully requested.

Claims 1-10 and 12-16 are rejected as allegedly obvious over Brown US 3,236,735 in view of Ruddy US 5,466,440 and Weaver US 3,935,099. The rejection is respectfully traversed.

Ruddy relates to the use of barium sulfate formulations to image the gastrointestinal tract of patients. Ruddy's formulations include a polymeric surfactant and a smectite clay, which improve adhesion to the GI mucosa, in contrast with the presently claimed compositions that flocculate and mark the stool. As for the other references cited in the present Office Action, Ruddy is concerned with dispersing barium sulfate rather than flocculating it. At column 1, line 20 Ruddy indicates that barium sulfate is usually administered as a solution that has limited stability even with the addition of stabilisers. Ruddy goes on to state that barium sulfate "often forms clumps that

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yield resultant radio opaque areas on x-ray films and has poor patient acceptability characteristics". Ruddy teaches the use of bioadhesive surfactants (which are dispersants) with a view to stabilizing the suspension, i.e. to prevent flocculation.

Weaver is cited for the use of sonication to treat a barium sulfate composition; however, Weaver relates to methods of reducing the water content of emulsions, suspensions and dispersants with highly absorbent starch containing polymeric compositions. This is not in the field of imaging, and the Weaver abstract indicates that the compositions therein may be useful in things such as surgical pads, sheets and paper towels. An isolated disclosure in the material about starch is certainly not going to fall within the ambit of a person skilled in the art in the field of formulating solutions or mixtures for gastric imaging, or to a person who is interested in gastric imaging. There does not appear to be an appropriate motivation for combining Weaver with Brown and Ruddy.

As discussed above, the defect of Brown is not cured by either Weaver or Ruddy. At best the combined references teach compositions for dispersal of barium sulfate within the GI system, those compositions having certain properties of mucosal adhesion associated with a combination of polymeric surfactants

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with smectite clay. However, those compositions still lack the properties of low flocculation resistance and being substantially free of ionic dispersants required by the present claims. Further, with respect to method claims 12-15, the references again fail to teach or suggest the marking of stool as required by the claims. Therefore, because the cited references, either alone or in combination, fail to teach or suggest every limitation of the present claims, they do not render the claims obvious. The withdrawal of this rejection is respectfully requested.

Claims 1-4, 6-8, 10 and 12-18 are rejected as allegedly obvious over Brown US 3,236,735 in view of Kaufman US 6,331,116. The rejection is respectfully traversed.

Kaufman is cited for teaching the administration of barium sulfate over 24-48 hours to cleanse the colon prior to imaging by a CT scan. However, the barium sulfate formulation taught by Kaufman (see, e.g., column 16, line 45) is a conventional, non-flocculating imaging agent. Thus, as before, Kaufman does not cure the defect of Brown, and the cited references, either alone or in combination, fails to teach or suggest the compositions or methods of the present claims, which require that the barium sulfate

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composition be substantially free of ionic dispersants and have low flocculation resistance. The withdrawal of the rejection is respectfully requested.

The Examiner is encouraged to telephone the undersigned attorney to discuss any matter that would expedite allowance of the present application.

Respectfully submitted,

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